Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 05-22-2015.

Submission # 5

As of 5-11-2015, this request has been rejected for oral testimony.

NOVARTIS

May 6, 2015

Tammy Haugland BS
hauglant@dhw.idaho.gov

Dear Ms. Tammy Haugland,

Your Regl Acct Msl, Assoc Dir Mary Kemhus,has forwarded to us your request for information regarding Gilenya™ (fingolimod).

The Novartis Medical Information department provides responses to unsolicited requests for information from health care professionals. This response is for your medical information purposes only and should not be regarded as a recommendation by Novartis Pharmaceuticals Corporation.

For marketed products, the information provided herein may be outside of the approved product labeling. Please refer to the package insert for full prescribing information. However, if the information you requested pertains to a compound in development, please note that the compound is not currently FDA approved for use in the United States.

In this document, please find the response(s) to your question:

- GILENYA - Medical Literature Request
- Medical Literature Requests:
    - Kappos L, O'Connor P, Radue EW. Long-term effects of fingolimod in multiple sclerosis: The randomized FREEDOMS extension trial. Neurology. 2015 Apr 14;84(15):1582-91.
    - Kappos L, Cohen J, et al. Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings. Multiple Sclerosis and Related Disorders(2014) 3, 494%uFFFD504.

For marketed products, the end of this document includes the FDA-approved indication(s) and general safety information for the product(s) referenced above.

Novartis Medical Information is Available on the Web, 24/7

The newly redesigned Medical Information website and mobile applications are now available to get access to Novartis product information. The advanced functionality of both of these offer simple navigation, robust search features, bookmarking, prescribing information and the ability to directly submit inquiries to our Medical Information Department – all tailored to meet your needs in a timely manner. For information about Novartis products, please visit https://medinfo.novartispharmaceuticals.com or search for Novartis at your mobile applications store (available for iPhone, iPad, Android and Windows Phone devices).

Please contact us if you have additional questions at 1-(888)-NOW-NOVA. Full prescribing information on Novartis marketed products is available on our website at http://www.pharma.us.novartis.com/products/bybrand.shtml

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Sincerely,

Madhavi Patel
Medical Information Spec
Medical Information and Communication

Inquiry Number(s): FMAV-01843730

Tammy Haugland BS

May 6, 2015

Medical Literature Request

In response to your request, please find the enclosed Medical Literature.

Copyright
If you are receiving this article electronically, please note that the attached article(s) has been provided at your request and copyright permission has been secured for your personal use based on your medical inquiry request. You are permitted to print one copy for your personal use then delete the electronic attachment. The article(s) may not be electronically stored, distributed, transmitted or altered. Opening the attachment(s) constitutes an acceptance of the Terms of Use. If you do not accept the Terms of Use, please delete the attachment(s) without opening it.

Product Description
Gilenya (fingolimod) is a sphingosine-1-phosphate receptor modulator available as an oral capsule.

Indication
Gilenya is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Gilenya is not indicated for the treatment of non-relapsing forms of multiple sclerosis. Gilenya should not be started in patients with active or chronic infections until the infection(s) is resolved.

Contraindications
Gilenya is contraindicated in the following:

- Patients who, in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III/IV heart failure
- A history or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker
- A baseline QTc interval >500msec
- Treatment with Class Ia or Class III anti-arrhythmic drugs

Gilenya is not indicated for other disease states. Please refer to the Gilenya full prescribing information.
Novartis, in collaboration with the Food and Drug Administration (FDA), developed a Risk Evaluation and Mitigation Strategy (REMS) for Gilenya (fingolimod). Please review the full Prescribing Information for detailed safety information for Gilenya.
You can access an electronic copy of the REMS components by using the links provided below:
http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/assets/pdf/REM/Gilenya_ProfessionalSociety_letter.pdf
http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/assets/pdf/REM/Gilenya_HCP_Safety_Information_Guide.pdf
http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/assets/pdf/REM/Gilenya_HCP_letter.pdf
The REMS components may also be accessed on the Gilenya REMS website(www.gilenyarems.com)

May 1, 2015

Idaho Medicaid Pharmacy & Therapeutics Committee
Attention: Tami Eide, Pharm.D.
3232 Elder Street
Boise, Idaho 83705

Dear Dr. Eide,

In response to your unsolicited request for information, I am forwarding two studies and a summary of key points related to the safety and efficacy of Gilenya (fingolimod). These studies were not included in the posted monograph and provide additional data to support long term safety and efficacy of Gilenya.

Kappos et al. Fingolimod in relapsing multiple sclerosis: an integrated analysis of safety findings

- This publication reports safety findings from phase 2/3 studies, associated extensions and post-marketing experience up to December 2011, including patients who have received treatment for more than seven years.
- The overall incidence of adverse events and serious adverse events was similar in patients who received the approved dose of fingolimod (0.5 mg) and those who received placebo in the FREEDOMS trial.
- There was a similar rate of drug discontinuation due to adverse events between fingolimod and placebo groups, indicating that at the approved dose, adverse events have a limited impact on tolerability and adherence.
- The safety profile of fingolimod has been well characterized and this publication helps to consolidate available safety information.

Kappos et al. Long-term effects of fingolimod in multiple sclerosis

- This trial was designed to determine if treatment effects of fingolimod are sustained beyond two years and if switching from control to active therapy replicates efficacy.
- Patients switching to fingolimod (from placebo) experienced fewer relapses, Gd-enhancing lesions and T2 lesions after switching.
- Patients randomized to fingolimod initially retained the benefits of earlier treatment (lower annualized relapse rate, fewer patients with confirmed disability progression).
- No new safety findings were observed in this extension compared with the two year controlled trial.

Please consider for testimony on May 22nd.

Thank you,

Mary Kemhus, PharmD
Regional Account MSL
Novartis Pharmaceuticals

Long-term effects of fingolimod in multiple sclerosis

The randomized FREEDOMS extension trial

OPEN

Ludwig Kappos, MD
Paul O'Connor, MD
Ernst-Wilhelm Radue, MD
Chris Polman, MD
Reinhard Hohlfeld, MD
Krzysztof Selmaj, MD
Shannon Ritter, MS
Rolf Schlosshauer, MSc
Philipp von Rosenstiel, MD
Lixin Zhang-Auberson, MD
Gordon Francis, MD

Correspondence to Professor Kappos: lkappos@uhbs.ch

ABSTRACT

Objective: To assess long-term safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: Patients completing FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) were eligible for this dose-blinded, parallel-group extension study, continuing fingolimod 0.5 mg/day or 1.25 mg/day, or switching from placebo to either dose, randomized 1:1. Efficacy variables included annualized relapse rate (ARR), brain volume loss (BVL), and confirmed disability progression (CDP). Between-group analyses were conducted in the intent-to-treat (ITT) population from FREEDOMS baseline to end of study. Within-group analyses compared years 0–2 (FREEDOMS) and years 2–4 (extension) in the extension ITT population.

Results: Of 1,272 patients (FREEDOMS ITT population), 1,033 were eligible, and 920 enrolled in the extension study (continuous-fingolimod: 0.5 mg [n = 331], 1.25 mg [n = 289]; placebo-fingolimod: 0.5 mg [n = 155], 1.25 mg [n = 145]); 916 formed the extension ITT population (n = 330; n = 287; n = 154; n = 145) and 773 (84%) completed. In the continuous-fingolimod groups, ARR was lower ($p < 0.0001$), BVL was reduced ($p < 0.05$), and proportionately more patients were free from 3-month CDP ($p < 0.05$) than in a group comprising all placebo-fingolimod patients. Within each placebo-fingolimod group, ARR was lower ($p < 0.001$, both) and BVL was reduced after switching ($p < 0.01$, placebo-fingolimod 0.5 mg). Rates and types of adverse events were similar across groups; no new safety issues were reported.

Conclusion: Efficacy benefits of fingolimod during FREEDOMS were sustained during the extension; ARR and BVL were reduced after switching.

Classification of evidence: This study provides Class IV evidence that long-term fingolimod treatment is well-tolerated and reduces relapse rates, disability progression, and MRI effects in patients with RRMS. ***Neurology*® 2015;84:1582–1591**

GLOSSARY

AE = adverse event; **ARR** = annualized relapse rate; **BVL** = brain volume loss; **CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **EoS** = end of study; **FREEDOMS** = FTY720 Research Evaluating Effects of Daily Oral Therapy in MS; **Gd** = gadolinium; **HR** = hazard ratio; **ITT** = intent-to-treat; **MS** = multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **TRANSFORMS** = Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting MS.

Fingolimod (FTY720), a sphingosine 1-phosphate receptor modulator, is the first oral disease-modifying therapy approved for the treatment of relapsing multiple sclerosis (MS).[1,2] Clinical efficacy was investigated in 3 double-blind, randomized, phase 3 trials in patients with relapsing-remitting MS (RRMS): Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting MS (TRANSFORMS), FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS), and FREEDOMS II.[3–5]

Supplemental data at Neurology.org

From the Department of Neurology (L.K.), University Hospital, Basel, Switzerland; St. Michael's Hospital (P.O.'C.), Toronto, Canada; Medical Image Analysis Centre (E.-W.R.), University Hospital, University of Basel, Switzerland; Department of Neurology (C.P.), VU University Medical Center, Amsterdam, Netherlands; Ludwig-Maximilians University of Munich and Munich Cluster for Systems Neurology (SyNergy) (R.H.), Germany; Department of Neurology (K.S.), Medical University of Lodz, Poland; Novartis Pharmaceuticals Corporation (S.R., G.F.), East Hanover, NJ; and Novartis Pharma AG (R.S., P.v.R., L.Z.-A.), Basel, Switzerland.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by the study sponsor, Novartis Pharma AG, Basel, Switzerland.

In TRANSFORMS, fingolimod reduced annualized relapse rate (ARR) at 1 year by 52% compared with IM interferon-β-1a, and showed significant benefits on MRI outcomes, including brain atrophy.[3] In the 24-month placebo-controlled FREEDOMS trial, fingolimod 0.5 mg significantly reduced ARR (0.18 vs 0.40 on placebo; $p < 0.001$), disability progression (hazard ratio 0.70; $p = 0.02$), MRI lesion activity (number of new or enlarged lesions on T2-weighted images, gadolinium [Gd]-enhancing lesions; $p < 0.001$ for all), and brain atrophy (brain volume loss [BVL] at 2 years, −0.84% vs −1.31% on placebo; $p < 0.001$).[4] Fingolimod 0.5 mg also significantly reduced ARR, MRI measures, and brain atrophy over 2 years in the FREEDOMS II trial.[5] The FREEDOMS II trial was similar in design and objectives to FREEDOMS, except it included additional measures (e.g., Holter monitoring) at the request of the Food and Drug Administration.[5] We report results from the FREEDOMS trial extension, the objective of which was to evaluate the long-term efficacy, safety, and tolerability of fingolimod in patients with RRMS.

METHODS

Study oversight and design. Study oversight and steering committee members have been reported previously.[4] This extension study consisted of a dose-blinded, parallel-group phase and an open-label phase; the study was to continue until drug approval and availability. A protocol amendment stopping use of fingolimod 1.25 mg in all MS clinical studies was made in November 2009, when unblinding of the FREEDOMS trial revealed higher discontinuation rates following an adverse event (AE) and little efficacy benefit associated with the 1.25-mg dose compared with the 0.5-mg dose.[4] Following this amendment, all patients began to transfer to the open-label phase, receiving fingolimod 0.5 mg/day. Between June 2010 and June 2011, patients who had participated in the phase 2[6,7] and phase 3[3–5] clinical trials could migrate from the respective extension studies to continue on fingolimod 0.5 mg in a separate open-label study (LONGTERMS [ClinicalTrials.gov number NCT01281657]).

Standard protocol approvals, registrations, and patient consents. All patients who completed the 24-month FREEDOMS trial were eligible for the extension (ClinicalTrials.gov number NCT00662649); locations and eligibility criteria for FREEDOMS have been described.[4] Exclusion criteria included discontinuation of study drug due to an AE or onset of chronic immune system disease requiring immunosuppressive treatment during FREEDOMS. All patients gave written informed consent. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and with the Declaration of Helsinki.[8,9] The protocol and all amendments were approved by each site's institutional review board/independent ethics committee.

Randomization and masking. The randomization procedure used in FREEDOMS has been described.[4] Patients who received fingolimod in FREEDOMS continued on the same blinded dose in the extension. Patients who received placebo in FREEDOMS were re-randomized (1:1) to oral fingolimod 0.5 mg or 1.25 mg once daily in the extension; a separate medication randomization list was produced by the study sponsor, using a validated system that automated the random assignment of medication numbers to medication packs containing the study drug. Patients, investigators, site personnel, independent evaluating physicians, and first dose administrators remained blinded to the treatment dose until the implementation of the protocol amendment. During the dose-blinded phase, study drug was packaged in a blinded fashion and was dispensed by the investigator according to patients' randomization numbers. Thereafter, all patients received open-label fingolimod 0.5 mg once daily, but remained blinded to their treatment assignment during FREEDOMS.

Procedures and assessments. In order to maintain blinding of drug assignment during FREEDOMS, all patients were monitored by an independent physician following their first dose of drug in the extension, which was taken the day after the last dose during FREEDOMS. Definitions for ARR and disability progression have been reported.[4] Relapse and safety assessments were scheduled at months 24.5, 25, 26, and 27, and then every 3 months. Expanded Disability Status Scale (EDSS) score was assessed every 3 months by a specially trained and certified independent physician not involved in the patients' care.[10] Standardized MRI scans were obtained every 12 months and processed centrally at the MS MRI Evaluation Center (Basel, Switzerland). Relapse, safety, EDSS assessments, and MRI scans were also obtained at the end of the extension and at follow-up visits. Safety was overseen by an independent data and safety monitoring board. Details of clinical and MRI assessments are given in the supplemental data on the *Neurology*® Web site at Neurology.org.

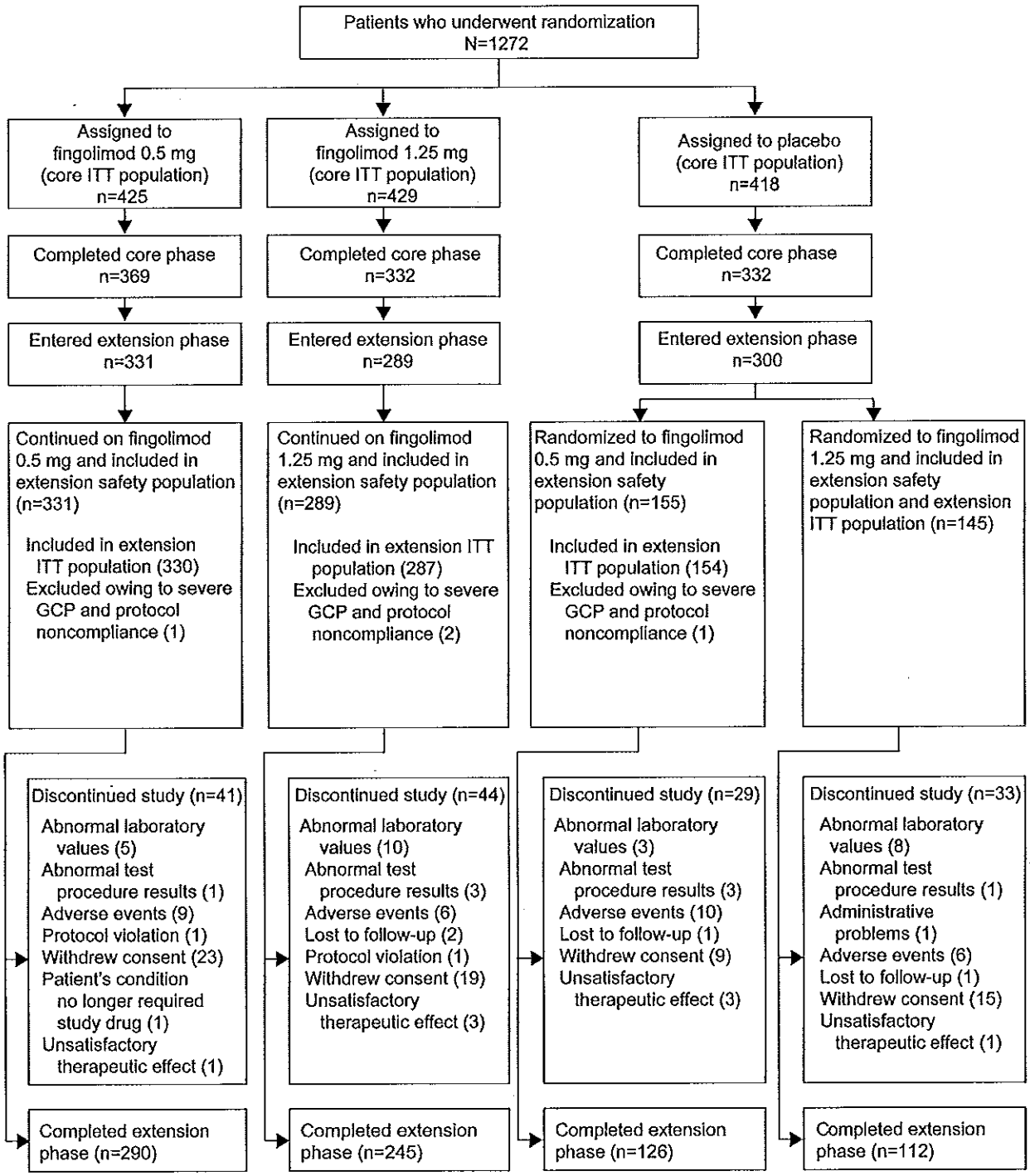
Statistical analysis. Sample size was based on the number of patients who entered the extension rather than statistical power calculation. Between-group comparisons of the effects of continuous vs delayed initiation of fingolimod therapy were evaluated in the FREEDOMS intent-to-treat (ITT) population (all patients randomized in FREEDOMS who received at least one dose of study drug, including patients who did not enter the extension study). Comparisons were made for outcomes assessed from FREEDOMS baseline (month 0) to end of study (EoS), between continuously treated patients (continuous fingolimod 0.5 mg or 1.25 mg groups) and all patients who switched from placebo to fingolimod (combined switch group). Within-group comparison of treatment effects between months 0 and 24 (during FREEDOMS) and months 24 and 48 (during the extension) was made in the extension ITT population (all randomized patients who received at least one dose of extension study drug) and in the subgroup of patients within the extension ITT population who completed 48 months of therapy (48-month completer population). Baseline characteristics and safety outcomes were assessed using descriptive statistics. Extension-phase efficacy analyses were exploratory and 2-sided (significance level, 0.05), with no adjustment for multiple analyses. Details of statistical tests used for between-group and within-group analyses are given in the supplemental data.

Classification of evidence. Given that safety and efficacy were demonstrated in FREEDOMS, the extension phase was designed to determine if treatment effects are sustained beyond 2 years, if

switching from control to active therapy replicates this efficacy, and whether late-onset safety events occur. This study provides Class IV evidence that daily fingolimod 0.5 mg is well-tolerated in the long term, with no late-onset safety events. Patients switching to fingolimod experienced fewer relapses, Gd-enhancing lesions, and T2 lesions (all $p < 0.001$) after switching. When compared over the whole observation period with those initially randomized to placebo, patients initially randomized to fingolimod retained the benefits of earlier treatment: lower ARR ($p < 0.0001$), proportionately fewer patients with confirmed disability progression ($p < 0.05$), fewer Gd-enhancing and T2 lesions ($p < 0.0001$), and less BVL ($p < 0.05$).

RESULTS Of 1,272 patients randomized (FREEDOMS ITT population), 1,033 (81%) completed FREEDOMS and were eligible for the extension;

Figure 1 Patient disposition



Reasons for discontinuation from FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) were reported previously.[4] Only those patients who completed FREEDOMS were eligible to enter the extension phase; 38 patients in the fingolimod 0.5 mg group, 43 in the fingolimod 1.25 mg group, and 32 in the placebo group decided not to participate in the extension. GCP = good clinical practice. ITT = intent to treat.

Table 1 Demographic and clinical characteristics at entry to FREEDOMS (extension safety population)

Characteristic	Placebo–fingolimod 0.5 mg (n = 155)	Placebo–fingolimod 1.25 mg[a] (n = 145)	Continuous fingolimod 0.5 mg (n = 331)	Continuous fingolimod 1.25 mg[a] (n = 289)
Female, n (%)	106 (68.4)	107 (73.8)	234 (70.7)	204 (70.6)
Previous MS treatment, n (%)	60 (38.7)	53 (36.6)	137 (41.4)	106 (36.7)
Age, y	38.1 (8.3); 37 (18–55)	36.6 (9.2); 35 (19–55)	36.5 (8.6); 36 (18–55)	37.2 (8.9); 38 (17–55)
Time from first MS symptom, y	7.8 (5.9); 7 (1–28)	8.4 (7.1); 6 (0–32)	8.0 (6.6); 7 (0–34)	8.2 (6.7); 7 (0–29)
Relapses in 1 y before enrollment	1.4 (0.6); 1 (0–3)	1.5 (0.9); 1 (0–6)	1.5 (0.8); 1 (0–5)	1.5 (0.8); 1 (0–6)
Relapses in 2 y before enrollment	2.1 (1.1); 2 (1–7)	2.2 (1.4); 2 (1–10)	2.2 (1.2); 2 (1–11)	2.1 (1.3); 2 (1–10)
EDSS score	2.4 (1.3); 2.0 (0.0–5.5)	2.4 (1.2); 2.0 (0.0–5.5)	2.3 (1.3); 2.0 (0.0–5.5)	2.4 (1.3); 2.0 (0.0–5.5)
Gd-enhancing lesion count	1.1 (2.3); 0 (0–18)	1.1 (2.7); 0 (0–25)	1.5 (4.0); 0 (0–37)	1.7 (4.0); 0 (0–26)
Volume of T2 lesions, mm³	5,659 (6,775); 2,958 (0–35,523)	5,971 (6,508); 3,236 (0–29,709)	6,458 (7,844); 3,276 (0–47,148)	7,406 (9,125); 3,577 (0–43,580)
Normalized brain volume, mL	1,516 (79.6); 1,523 (1,315–1,723)	1,513 (86.4); 1,515 (1,251–1,716)	1,521 (80.9); 1,528 (1,171–1,733)	1,516 (90.6); 1,516 (1,217–1,764)

Abbreviations: EDSS = Expanded Disability Status Scale; FREEDOMS = FTY720 Research Evaluating Effects of Daily Oral Therapy in MS; Gd = gadolinium; MS = multiple sclerosis.
[a] All patients receiving fingolimod 1.25 mg/day were switched to fingolimod 0.5 mg/day after the 1.25 mg/day dose was discontinued from all MS clinical studies. Continuous variables are presented as mean (SD) and median (range).

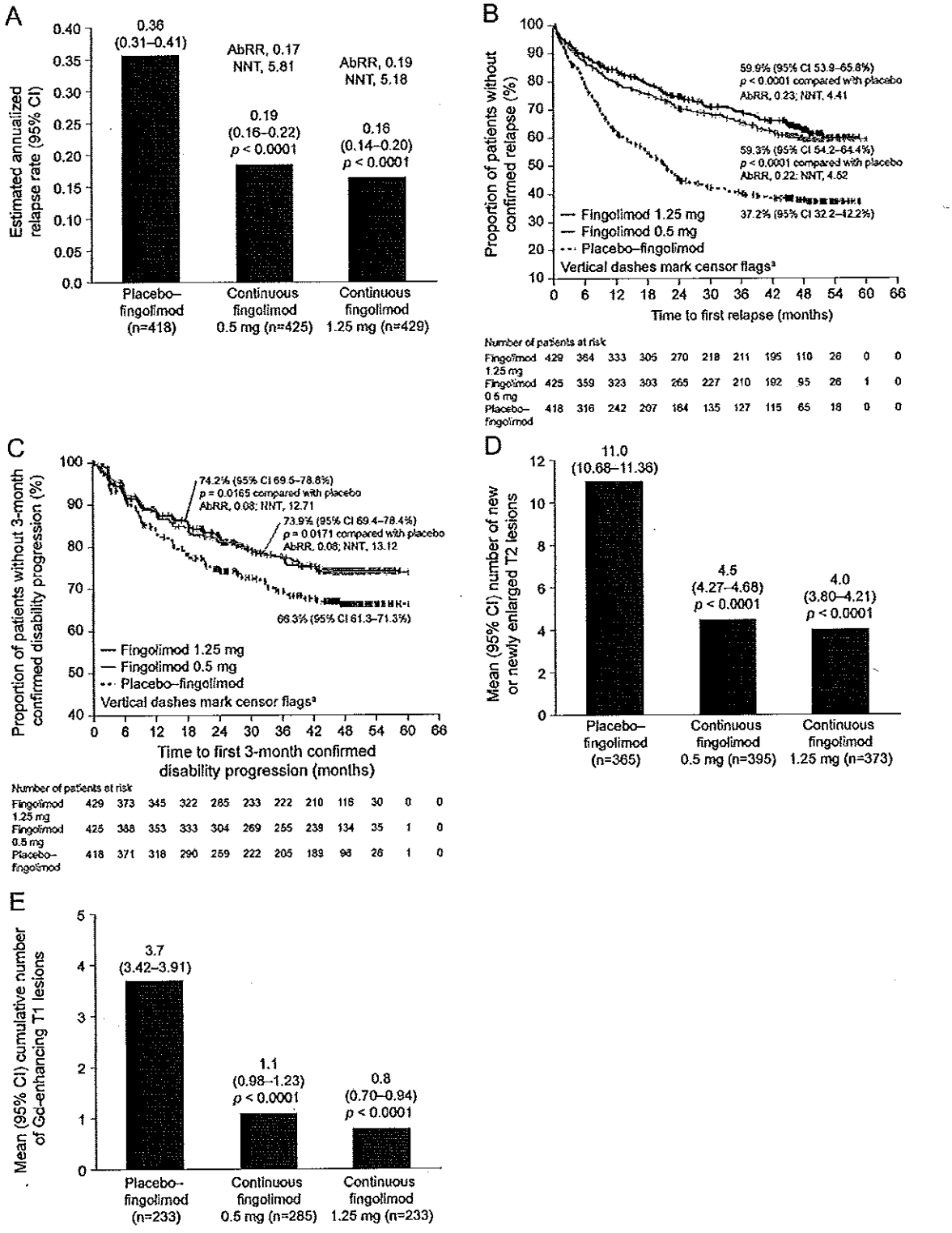
920 patients (89%) entered the extension (extension safety population), 916 (99.6%) of whom formed the extension ITT population, and 773 (84%) completed. Patient flow by treatment group and reasons for discontinuation are shown in figure 1; a data summary of patients who chose not to enroll is included in the supplemental data. At FREEDOMS baseline, disease and patient characteristics in the extension ITT population were similar across treatment groups, although the mean number of Gd-enhancing T1 lesions and T2 lesion volumes were slightly higher in the continuous fingolimod than in the switch groups (table 1). Baseline characteristics of the 48-month completer population (table e-1) and of the extension ITT population were similar.

The FREEDOMS study ran from 2005 to 2009 and the extension ran from February 2008 to June 2011. Time spent in the extension depended on the time of enrollment and when migration to LONGTERMS commenced at each study site. Over 90% of patients (856/920) completed 12 months of treatment in the extension (i.e., attended the month 36 visit), 88% (811/920) reached month 42, 44% (402/920) reached month 48, and 9% (87/920) reached month 54. The respective mean (SD) duration of exposure to fingolimod in the extension safety population was 1,394 (208) and 1,372 (225) days in the continuous fingolimod 0.5 mg and 1.25 mg groups, and 669 (206) and 626 (248) days in the placebo–fingolimod 0.5 mg and 1.25 mg switch groups.

Efficacy. From month 0 to EoS, ARR in the continuous fingolimod groups was lower than in the combined switch group (figure 2A), corresponding to reductions of 48% (ARR ratio 0.52 [95% confidence interval (CI) 0.42–0.64]) and 54% (ARR ratio 0.46 [95% CI 0.37–0.57]) for the fingolimod 0.5 mg and 1.25 mg doses, respectively (both $p < 0.0001$). Similar advantages favoring the continuous fingolimod groups over the combined switch group were seen for the proportion of relapse-free patients at EoS and for the risk of relapse from month 0 to EoS (figure 2B). Comparing months 24–48 with months 0–24 within group in the extension ITT population, ARRs were significantly reduced in both switch groups, and remained low in the continuous fingolimod groups (table e-2). When the same within-group comparison was made in the 48-month completer population, the reduction in ARR was significant in the placebo–fingolimod 0.5 mg switch group ($p < 0.0001$), and showed a trend toward reduction in the placebo–fingolimod 1.25 mg switch group ($p = 0.0643$).

At EoS, the proportions (95% CI) of patients free from 3-month (figure 2C) and 6-month confirmed disability progression in the continuous fingolimod groups were 74% (69%–78%) and 80% (76%–84%) in the

Figure 2 Between-group comparisons (month 0 to end of study, FREEDOMS ITT population)



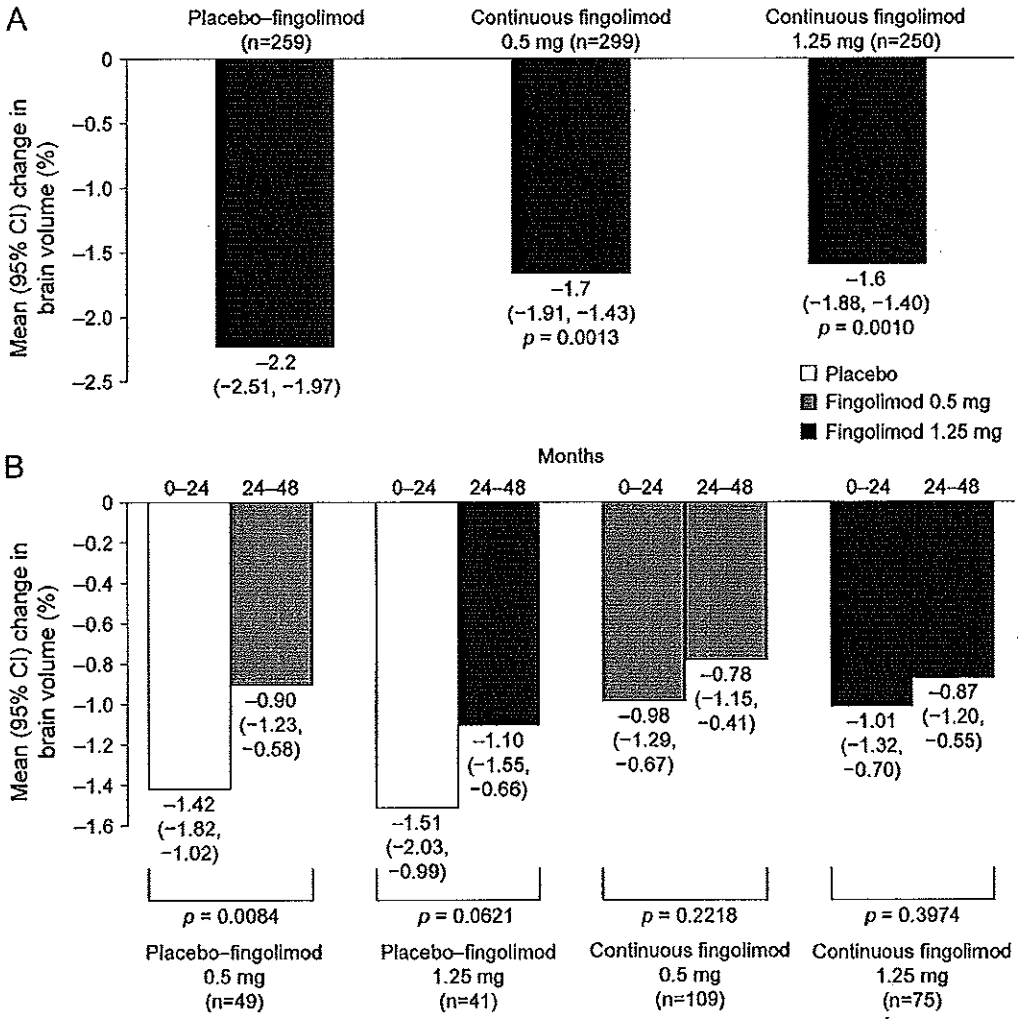
(A) Annualized relapse rate (ARR) estimated from a negative binomial model adjusted for treatment, pooled country, number of relapses in the 2 years before enrollment, and FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) baseline Expanded Disability Status Scale score; *p* values are for the ARR ratio between active treatment ARR and placebo ARR. (B) Time to first confirmed relapse with Kaplan-Meier estimate of patients free from relapse at end of study (EoS). [a]Censor flags indicate the time in study for patients with no confirmed relapse during the time interval, patients for whom follow-up ended before a confirmed relapse occurred, and patients who dropped out prior to a relapse. (C) Time to 3-month confirmed disability progression based on EDSS score with Kaplan-Meier estimate of patients free from progression at EoS. (D) Cumulative number of new or newly enlarged T2 lesions compared using a negative binomial model adjusted for treatment, FREEDOMS baseline volume of T2 lesions, and pooled country. (E) Cumulative number of gadolinium (Gd)-enhancing T1 lesions from month 0 to EoS, including patients with all assessments during that time interval; *p* values are for comparisons with the placebo-fingolimod group. AbRR = absolute risk reduction; CI = confidence interval; NNT = number needed to treat.

0.5 mg group, 74% (70%–79%) and 79% (75%–84%) in the 1.25 mg group, and 66% (61%–71%) and 73% (68%–77%) in the combined switch group. Compared with the combined switch group, the respective risk of disability progression confirmed after 3 months and 6 months was reduced by 27% (hazard ratio [HR] 0.73 [95% CI 0.56–0.95]; $p = 0.0189$) and 31% (HR 0.69 [95% CI 0.51–0.93]; $p = 0.0140$) in the continuous fingolimod 0.5 mg group and by 29% (HR 0.71 [95% CI 0.55–0.93]; $p = 0.0138$) and 30% (HR 0.70 [95% CI 0.52–0.95]; $p = 0.0211$) in the continuous fingolimod 1.25 mg group.

From day 0 to EoS, BVL was significantly lower in the continuous fingolimod 0.5 mg and 1.25 mg groups than in the combined switch group (figure 3A). For analysis of BVL, evaluable patients in the extension ITT population coincided with those evaluable in the 48-month completer population. In this group, the rate of BVL during months 24–48 was lower after switching to fingolimod 0.5 mg, and showed a trend toward reduction after switching to 1.25 mg compared with months 0–24 on placebo. During months 24–48, there were no differences among the 4 treatment groups in rates of brain volume reduction (figure 3B).

The mean number of new or newly enlarged T2 lesions from month 0 to EoS was significantly lower in both continuous treatment groups than in the combined

Figure 3 Percentage brain volume change



(A) Between-group comparisons of changes in brain volume from month 0 to end of study in the FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) intent-to-treat (ITT) population. Percentage brain volume change was compared using a rank analysis of covariance adjusted by treatment, normalized brain volume at FREEDOMS baseline, and country. (B) Within-group comparisons (months 24–48 vs months 0–24) in the extension ITT population and 48-month completer subgroup. Comparisons were made with the Wilcoxon signed-rank test. All patients receiving fingolimod 1.25 mg/day were switched to fingolimod 0.5 mg/day after the 1.25 mg/day dose was discontinued from all multiple sclerosis clinical studies. In this analysis, the evaluable individuals in the extension ITT population coincided with those evaluable in the 48-month completer subgroup; therefore the findings shown represent those for both groups. n = number of patients with brain volume change data for both time periods. CI = confidence interval.

switch group (figure 2D). The cumulative mean number of Gd-enhancing T1 lesions from month 0 to EoS was also significantly lower in the continuous fingolimod groups than in the combined switch group (figure 2E). In each switch group in the extension ITT population, there was a significant reduction in the mean number of Gd-enhancing T1 lesions and of new or newly enlarged T2 lesions, and a significant increase in the proportion of patients free from Gd-enhancing T1 lesions or new or newly enlarged T2 lesions during months 24–48 compared with months 0–24 (table e-2). The clinical and MRI outcomes of the 48-month completers (table e-3) were similar to those of the FREEDOMS ITT population during the FREEDOMS study.[4]

Table 2 Adverse events (extension safety population)

Adverse event, n (%)	Placebo-fingolimod 0.5 mg (n = 155)	Placebo-fingolimod 1.25 mg[a] (n = 145)	Continuous fingolimod 0.5 mg (n = 331)	Continuous fingolimod 1.25 mg[a] (n = 289)
Any AE	148 (95.5)	133 (91.7)	314 (94.9)	272 (94.1)
Infection	109 (70.3)	100 (69.0)	240 (72.5)	204 (70.6)
Cardiac disorder	10 (6.5)	6 (4.1)	19 (5.7)	19 (6.6)
Abnormally elevated hepatic enzymes	20 (12.9)	28 (19.3)	24 (7.3)	24 (8.3)
AE leading to study drug discontinuation	14 (9.0)	14 (9.7)	15 (4.5)	16 (5.5)
Most commonly reported AEs[b]				
Nasopharyngitis	44 (28.4)	39 (26.9)	84 (25.4)	82 (28.4)
URT infection	24 (15.5)	23 (15.9)	58 (17.5)	39 (13.5)
Lymphopenia	17 (11.0)	19 (13.1)	52 (15.7)	52 (18.0)
Headache	26 (16.8)	18 (12.4)	41 (12.4)	27 (9.3)
Influenza	12 (7.7)	9 (6.2)	33 (10.0)	30 (10.4)
Lymphocyte count decrease	14 (9.0)	12 (8.3)	16 (4.8)	29 (10.0)
ALT increase	9 (5.8)	16 (11.0)	11 (3.3)	10 (3.5)
SAEs[c]				
Any SAE	11 (7.1)	17 (11.7)	31 (9.4)	31 (10.7)
Hepatobiliary disorders	0	0	0	2 (0.7)
Cholelithiasis	0	0	0	2 (0.7)
Infections/infestations	1 (0.6)	2 (1.4)	8 (2.4)	8 (2.8)
Appendicitis	0	0	2 (0.6)	1 (0.3)
Neoplasms[d]	2 (1.3)	3 (2.1)	7 (2.1)	5 (1.7)
Basal cell carcinoma[e]	0	2 (1.4)	4 (1.2)	4 (1.4)
Uterine leiomyoma	0	0	2 (0.6)	0
CNS disorders	1 (0.6)	1 (0.7)	6 (1.8)	5 (1.7)
MS relapse	0	0	0	3 (1.0)
Epilepsy	0	0	2 (0.6)	0
Psychiatric disorders	0	4 (2.8)	2 (0.6)	1 (0.3)
Depression	0	2 (1.4)	0	0
Other AEs of special interest				
Herpesvirus infection	14 (9.0)	14 (9.7)	40 (12.1)	31 (10.7)
Sinus bradycardia	1 (0.6)	1 (0.7)	1 (0.3)	3 (1.0)
Bradycardia	1 (0.6)	2 (1.4)	1 (0.3)	2 (0.7)
Bradyarrhythmia	0	0	0	1 (0.3)
Macular edema	1 (0.6)	0	1 (0.3)	1 (0.3)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; MS = multiple sclerosis; SAE = serious adverse event; URT = upper respiratory tract.
[a] Patients on fingolimod 1.25 mg switched to fingolimod 0.5 mg after the 1.25 mg dose was discontinued.
[b] AEs by preferred term reported in 10% or more of patients in any treatment group during the extension.
[c] List contains total number of SAEs and lists separately all SAEs reported in ≥2 patients in any organ system class in any treatment group.
[d] Benign, malignant, and unspecified (including cysts and polyps).
[e] Including 3 SAEs reported after database lock.

Safety during the extension study. The proportions of patients experiencing any AE, infections/infestations, cardiac disorders, or serious AEs were broadly similar across all groups (table 2). The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection, lymphopenia, headache, and influenza (table 2). Abnormal hepatic enzyme levels were most common among patients switching to fingolimod 1.25 mg, and were more common in the switch groups than in the continuous fingolimod groups. Among AEs of special interest, there were 3 instances of macular edema, none of which was classified as serious. AEs leading to discontinuation of study drug occurred less frequently in the long-term continuous fingolimod groups than in the switch groups, and the most frequent events included lymphopenia, increased alanine aminotransferase, basal cell carcinoma, and dyspnea (each occurring in <1.4% of patients in any treatment group); there were no deaths.

Small increases in blood pressure were observed in patients in the switch groups, while blood pressure in patients in the long-term continuous treatment groups remained stable over time. Consistent with first-dose effects seen in FREEDOMS and with other previous clinical experiences,[4,11] a transient decrease in heart rate and a delay in atrioventricular conduction were observed in patients in the switch groups upon fingolimod initiation. Symptomatic first-dose bradycardia was seen in 2 patients, one with symptoms of severe dizziness and one with a mild feeling of cold. A transient episode of second-degree atrioventricular block on day 1 of therapy was reported in one patient who was asymptomatic and completed the extension study.

Five pregnancies were reported; 2 patients had normal, full-term pregnancies and delivered healthy babies. One patient had a therapeutic abortion when an ultrasound revealed that the fetus had tetralogy of Fallot. Another patient had a therapeutic abortion after an ultrasound revealed fetal death. One patient had an elective abortion.

DISCUSSION This extension of the pivotal FREEDOMS study provides robust evidence that the low level of disease activity seen with fingolimod during years 1 and 2 in FREEDOMS was sustained during years 3 and 4, suggesting persistence of the treatment effect. Overall, this study confirmed there was no relevant difference between the 2 fingolimod doses regarding clinical and MRI-related outcomes. Patients who started fingolimod during the extension experienced significant improvements in clinical and MRI measures, essentially replicating, in this within-group comparison, the findings from the between-group comparison in FREEDOMS. However, patients who were initially randomized to fingolimod and continued therapy for a mean period of approximately 46 months still retained an advantage based on clinical and paraclinical measures at EoS, compared with those who delayed starting treatment until the extension study. This observation both supports the evolving position in the MS community for early treatment and provides evidence for a continued effect of fingolimod for up to 4 years.

Fingolimod was the first MS treatment to demonstrate a beneficial effect on BVL in phase 3 studies compared with placebo,[4,5] and with IM interferon-β-1a.[3] The comparably low rates of BVL across all groups during this extension study are consistent with the assumption that the effect of fingolimod on this structural outcome is continuous and not confined to the treatment initiation phase. Further analyses and long-term observations must clarify the biological and functional implications of this effect.

The lack of a placebo-control group in our study limits conclusions regarding efficacy. Participants knew that the placebo arm had terminated, but their treatment assignment during FREEDOMS remained blinded, as did their dose, until all participants received fingolimod 0.5 mg. Personnel at the MRI evaluation center remain blinded to treatment assignment, with no access to individuals' clinical data. Bias could result from differential drop-out of patients experiencing a lack of efficacy or AEs during FREEDOMS, but notably, baseline characteristics among patients completing 48 months were comparable to those in the FREEDOMS ITT population. Similarly, bias could arise because approximately 11% of eligible patients chose not to enroll in the trial extension. Their reasons were not recorded, but an exploratory analysis comparing enrollers and nonenrollers is described in the supplemental data. Finally, the study was terminated before all patients reached month 48 on study medication. Therefore, periods for within-group comparisons varied, but this variation was similar across treatment groups.

No new safety findings were observed in this extension compared with the 2-year controlled trial. As expected, AEs associated with treatment initiation were increased in the switch group; however, the incidence of AEs, serious AEs, and AEs related to fingolimod's mode of action were similar across groups. The overall frequency of AEs was also similar across treatment groups in FREEDOMS, but AEs associated with discontinuation of treatment (primarily liver enzyme elevations) were more common in the fingolimod 1.25 mg group than in other groups.[4,12] This was not particularly evident in the extension; increased alanine aminotransferase was among the AEs that led to discontinuation, but this was recorded in all groups.

The lower percentage of patients who discontinued fingolimod owing to AEs in the continuous groups vs the switch groups may partly reflect selective drop-out of patients who experienced these AEs with fingolimod during FREEDOMS (cardiac AEs, macular edema, hepatic enzyme elevation),[4] but this also suggests good tolerability of long-term treatment, with no late-occurring, unexpected safety findings. This is supported by a recent safety analysis of several clinical studies of fingolimod in RRMS that included patients with over 7 years of exposure to the drug.[12] Cardiac effects associated with initiation of fingolimod were transient and have been reviewed extensively elsewhere.[13] Blood pressure increased slightly in patients initiating fingolimod during the extension, but remained stable in the continuous-treatment groups, suggesting that this effect occurs early with fingolimod and then plateaus after the first few months of treatment.[12,13]

In this extension study, we found continuously low disease activity among patients initially randomized to fingolimod, and significant improvements in clinical and MRI outcomes after patients switched to fingolimod from placebo. The fact that patients starting early on fingolimod retained the advantage gained in their first 2 years of treatment compared with those initially randomized to placebo accentuates the importance of early treatment and implies a continuous benefit of fingolimod on both clinical measures and BVL. In conjunction with the absence of new safety or tolerability issues, these findings support the value of fingolimod in the long-term treatment of RRMS.

AUTHOR CONTRIBUTIONS

Professor Kappos was involved in the design of the study, collection, analysis, and interpretation of the data, and drafting and revising the manuscript. Professor O'Connor was involved in the design of the study, collection, analysis, and interpretation of the data, and revising the manuscript. Professor Radue was involved in the design of the study, collection, analysis, and interpretation of the data, figure design, and revising the manuscript. Professor Polman was involved in the design of the study, collection and interpretation of the data, and revising the manuscript. Professor Hohlfeld was involved in the design of the study, interpretation of the data, and revising the manuscript. Professor Selmaj was involved in the design of the study, collection and interpretation of the data, and revising the manuscript. Dr. Ritter was the statistician responsible for analysis of the data and was involved in their interpretation, as well as drafting and revising the manuscript. Dr. Schlosshauer was responsible for operational aspects of the study, including collection of data and ensuring the study was conducted as mandated by the protocol, and was involved in analysis and interpretation of the data, and revising the manuscript. Dr. von Rosenstiel was involved in the design of the analysis plan, analysis and interpretation of the data, and revising the manuscript. Dr. Zhang-Auberson was involved in the design of the analysis plan, analysis and interpretation of the data, and writing and revising the manuscript. Dr Francis was involved in the design of the analysis plan, analysis and interpretation of the data, as well as planning, writing, and review of the manuscript.

ACKNOWLEDGMENT

The authors thank the patients and investigators who took part in this study; Peter Calabresi for participating in the steering committee; and Oxford PharmaGenesis Ltd. for editorial assistance, collating the comments of authors, and editing the paper for submission.

STUDY FUNDING

The study was sponsored by Novartis Pharma AG, Basel, Switzerland.

DISCLOSURE

L. Kappos: institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee, advisory board, and consultancy fees from Actelion, Addex, Bayer Health Care, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer Health Care, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; support of educational activities from Bayer Health Care, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva; royalties from Neurostatus Systems GmbH; and grants from Bayer Health Care, Biogen, Merck, Novartis, Roche, Swiss MS Society, the Swiss National Research Foundation, the European Union, and Roche Research Foundations. P. O'Connor: Abbott Labs, Actelion, Bayer, Biogen Idec, Celgene, EMD Merck Serono, Genentech, Genzyme, Lilly, Novartis, Roche, Sanofi-Aventis, and Teva Pharmaceuticals. Dr. O'Connor receives consultation fees from the MS Society of Canada. E.W. Radue: Actelion, Basilea Pharmaceutica Ltd., Biogen Idec, Merck Serono, and Novartis. C. Polman: Actelion, Biogen Idec, Bayer Schering, GlaxoSmithKline, Merck Serono, Novartis, Roche, Teva, and UCB. R. Hohlfeld: Bayer, Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis, and Teva. K. Selmaj: Novartis, Biogen Idec, Merck Serono, Roche, ONO Pharmaceuticals, and Genzyme. S. Ritter is an employee of Novartis Pharmaceuticals Corporation. R. Schlosshauer is an employee of Novartis Pharma AG. P. von Rosenstiel is an employee of Novartis Pharma AG. L. Zhang-Auberson is an employee of Novartis Pharma AG. G. Francis is an employee of Novartis Pharmaceuticals Corporation. Go to Neurology.org for full disclosures.

Received June 15, 2014. Accepted in final form December 19, 2014.

REFERENCES

1. Brinkmann V, Davis MD, Heise CE, et al. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J Biol Chem 2002;277:21453–21457.
2. Chun J, Brinkmann V. A mechanistically novel, first oral therapy for multiple sclerosis: the development of fingolimod (FTY720, Gilenya). Discov Med 2011;12:213–228.
3. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402–415.
4. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387–401.
5. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:545–556.
6. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006;355:1124–1140.
7. Comi G, O'Connor P, Montalban X, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler 2010;16:197–207.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed November 21, 2014.

9. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed November 21, 2014.
10. Neurostatus. Neurostatus training and documentation DVD for a standardized neurological examination and assessment of Kurtzke's functional systems and Expanded Disability Status Scale for MS patients. Available at: http://www.neurostatus.net. Accessed November 21, 2014.
11. European Medicines Agency. Gilenya EU summary of product characteristics (updated September 5, 2014). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf. Accessed November 21, 2014.
12. Kappos L, Cohen J, Collins W, et al. Fingolimod in relapsing multiple sclerosis: an integrated analysis of safety findings. Mult Scler Relat Disord 2014;3:494–504.
13. Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. Am Heart J 2014;168:632–644.

WriteClick® rapid online correspondence

The editors encourage comments about recent articles through WriteClick:

Go to *Neurology.org* and click on the "WriteClick" tab at the top of the page. Responses will be posted within 72 hours of submission.

Before using WriteClick, remember the following:

- WriteClick is restricted to comments about studies published in *Neurology* within the last eight weeks
- Read previously posted comments; redundant comments will not be posted
- Your submission must be 200 words or less and have a maximum of five references; reference one must be the article on which you are commenting
- You can include a maximum of five authors (including yourself)

Multiple Sclerosis and Related Disorders (2014) 3, 494-504

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/msard

Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings

Ludwig Kappos[a,*], Jeffrey Cohen[b], William Collins[c], Ana de Vera[c], Lixin Zhang-Auberson[c], Shannon Ritter[d], Philipp von Rosenstiel[c], Gordon Francis[d]

[a]*Neurology, Department of Medicine, Clinical Research and Biomedicine, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland*
[b]*Neurological Institute, The Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA*
[c]*Novartis Pharma AG, CH-4056 Basel, Switzerland*
[d]*Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07849-1080, USA*

Received 5 December 2013; received in revised form 28 February 2014; accepted 17 March 2014

KEYWORDS
Fingolimod;
Multiple sclerosis;
Safety;
Adverse events;
Cardiovascular events;
Pooled analysis

Abstract

Background: Fingolimod 0.5 mg once daily is the first approved oral therapy for relapsing multiple sclerosis (MS).

Objective: To report integrated long-term safety data from phase 2/3 fingolimod studies.

Methods: Descriptive safety data are reported from the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study, a 24-month, randomized, double-blind study comparing fingolimod 0.5 mg and 1.25 mg with placebo, and an All Studies group (patients who received fingolimod 0.5 mg (n=1640) or 1.25-0.5 mg (n=1776) in phase 2/3 studies and associated extensions). Relevant post-marketing experience, up to December 2011, is included.

Results: The incidence of adverse events (AEs) and serious AEs (SAEs) was similar with fingolimod and placebo in FREEDOMS. In the All Studies group, fingolimod 0.5 mg was associated with transient, rarely symptomatic (0.5%), bradycardia and second-degree atrioventricular block on treatment initiation, minor blood pressure increases, frequent (9%) but generally asymptomatic liver enzyme elevations, and macular oedema (0.4%). The incidences of infections (including serious and herpes infections), malignancies, SAEs and treatment discontinuations due to AEs were similar with fingolimod 0.5 mg and placebo.

Abbreviations: AV, atrioventricular; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; HPS, haemophagocytic syndrome; LRTI, lower respiratory tract infection; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; S1PR, sphingosine 1-phosphate receptor; TRANSFORMS, Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis; ULN, upper limit of normal

*Corresponding author. Tel.: +41 61 2654464.
E-mail address: ludwig.kappos@usb.ch (L. Kappos).

http://dx.doi.org/10.1016/j.msard.2014.03.002
2211-0348/

Conclusion: The safety profile of fingolimod has been well characterized in this large combined trial population. Although infrequent SAEs can occur, there is no increased risk of infections, malignancies or serious cardiovascular events versus placebo.

1. Introduction

Fingolimod (FTY720; Gilenya®, Novartis Pharma AG, Basel, Switzerland) is the first of a new class of therapeutic compounds - the sphingosine 1-phosphate receptor (S1PR) modulators (Brinkmann et al., 2010; Chun and Hartung, 2010). It is approved as a once-daily oral therapy at 0.5 mg for the treatment of relapsing forms of multiple sclerosis (MS) in many countries (European Medicines Agency, 2011; US Food and Drug Administration, 2010). S1PRs are expressed in many tissues, including cells of the immune, cardiovascular and central nervous systems (Brinkmann, 2007). In the immune system, modulation of S1PRs by fingolimod results in the retention of circulating lymphocytes in the lymph nodes, with a reversible reduction of peripheral blood lymphocyte counts to approximately 30% of pre-treatment values, which is postulated to reduce recirculation of autoreactive lymphocytes and to prevent infiltration into the central nervous system (Brinkmann et al., 2010; Chun and Hartung, 2010). Fingolimod treatment specifically retains naïve T cells and central memory T cells in the lymph nodes, while largely sparing effector memory T cells (Mehling et al., 2008; Pham et al., 2008), which are important in immune surveillance (Lanzavecchia and Sallusto, 2000).

Fingolimod has demonstrated superior efficacy to placebo as well as to the approved first-line therapy, intramuscular (IM) interferon beta-1a (Avonex®, Biogen Idec, Weston, MA, USA) in a phase 2 study and three phase 3 studies: FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS), FREEDOMS II and Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) in relapsing MS (Calabresi et al., in press; Cohen et al., 2010; Comi et al., 2010; Kappos et al., 2006, 2010; Khatri et al., 2011).

Here, we report safety data from an integrated analysis of FREEDOMS, FREEDOMS II, TRANSFORMS, the single MS phase 2 study and their extensions. In addition, we report deaths from the clinical development programme and post-marketing setting from May 2003 to December 2011, as well as other post-marketing safety cases of particular interest.

2. Materials and methods

2.1. Analysis groups

Results are reported from the following two analysis groups: the FREEDOMS group, which included all patients enrolled in the 2-year core phase of FREEDOMS (Kappos et al., 2010) (ClinicalTrials.gov identifier NCT00289978), and the All Studies group, which was an integrated analysis of safety data from all patients who received once-daily fingolimod in the 6-month, placebo-controlled, phase 2 core study (1.25 mg or 5.0 mg; ClinicalTrials.gov identifier NCT00333138), the 2-year phase 3 core studies (FREEDOMS, FREEDOMS II [0.5 mg or 1.25 mg; ClinicalTrials.gov identifier NCT00355134]) and the 1-year phase 3 core study TRANSFORMS (0.5 mg or 1.25 mg; ClinicalTrials.gov identifier NCT00340834), and their completed long-term extensions.

Following approval of fingolimod 0.5 mg, all patients receiving fingolimod 1.25 mg in study extensions were switched to fingolimod 0.5 mg (this group was referred to in the All Studies analysis as fingolimod 1.25-0.5 mg). Patients remained in study extensions until 31 March 2011 (database lock) or until the cut-off for the ongoing FREEDOMS II extension (Figure 1). Patients were then transferred to the ongoing, long-term observational safety study 2399 (ClinicalTrials.gov identifier NCT01281657).

Study methodologies for FREEDOMS, FREEDOMS II, TRANSFORMS and the phase 2 study have been previously reported in accordance with CONSORT guidelines (Cohen et al., 2010; Kappos et al., 2006, 2010; Khatri et al., 2011). The study design and entry criteria for FREEDOMS II closely match those of FREEDOMS. The FREEDOMS group provides a 24-month, placebo-controlled comparison with fingolimod, and the All Studies group provides fingolimod safety data from a larger population with longer follow-up. Data describing cardiovascular effects following treatment initiation come only from the phase 3 studies because data on these effects were not collected in a compatible manner during the phase 2 core study. All deaths are reported for patients exposed to fingolimod during May 2003-December 2011, including clinical trials and post-marketing data.

2.1.1. Outcome measures and analyses

Results are reported for the safety population, comprising all patients who received at least one dose of study drug. Safety analyses were summarized by means of descriptive statistics; numerical (not statistical) differences are described. The proportions of patients experiencing adverse events (AEs) and serious AEs (SAEs) are reported for the FREEDOMS group and the All Studies group (with a focus on the fingolimod 1.25-0.5 mg and 0.5 mg groups). Also reported in more detail are the following AEs of special interest: treatment initiation effects (pooled data from phase 3 studies only), infections, hypertension and notable increases in blood pressure, macular oedema, malignancies, liver enzyme effects and lymphopenia (FREEDOMS group; All Studies group). Patients were required to interrupt dosing if lymphocyte counts fell below a threshold ($<0.1 \times 10^9$/L initially, later increased to $<0.2 \times 10^9$/L at the request of the regulatory agency, but not due to any safety signal). Dosing could resume once lymphocyte counts reached 0.6×10^9/L. Due to a potential risk for teratogenesis, as seen in animals, fingolimod is not recommended for use in women who are, or want to become, pregnant. Full details of pregnancy outcomes and pregnancy risks are reported elsewhere

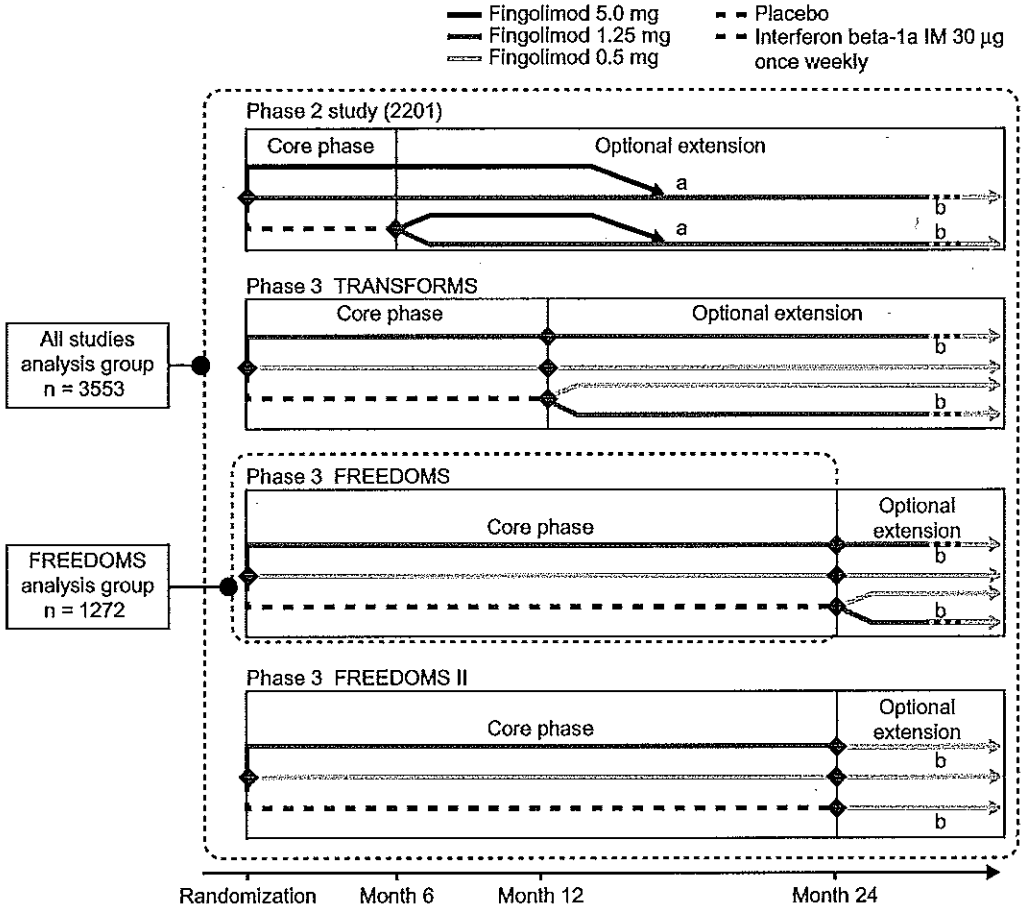


Figure 1 Analysis groups. (a) Patients who were initially randomized to fingolimod 5.0 mg during the phase 2 core study or extension were switched to fingolimod 1.25 mg during months 15-24 of the extension phase, then to fingolimod 0.5 mg between months 24 and 60. (b) All patients received fingolimod 0.5 mg in study extensions following approval of this dose. The All Studies analysis group includes all patients who switched from placebo or interferon beta-1a IM to fingolimod in the extension phases; the pooled treatment groups were fingolimod 0.5 mg (n=1640), fingolimod 1.25-0.5 mg (n=1776), fingolimod 5.0-1.25-0.5 mg (n=137, which included all patients who received fingolimod 5.0 mg only or fingolimod 5.0 mg then fingolimod 1.25 mg, before receiving fingolimod 0.5 mg). The FREEDOMS analysis group included patients receiving fingolimod 0.5 mg (n=425), fingolimod 1.25 mg (n=429) or placebo (n=418). FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; IM, intramuscular; TRANSFORMS, Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis.

(Karlsson et al., 2014), but otherwise are not further addressed in this article.

Additional methodological information for the studies in this analysis, including details of study oversight, inclusion and exclusion criteria, and blinding and randomization are provided in the Supplementary data.

3. Results

3.1. Study population

Baseline characteristics of patients in the phase 3 studies and the phase 2 study were similar among treatment groups (Calabresi et al., in press; Cohen et al., 2010; Kappos et al., 2006, 2010). The All Studies group comprised 3553 patients with MS, with 9070 patient-years of exposure to fingolimod, and included some patients with more than 7 years of exposure in the phase 2 extension study (as of 31 March 2011) (Table 1).

3.2. Incidence of adverse events and serious adverse events

In the FREEDOMS group, the overall relative risk of AEs (Figure 2) and the proportions of patients who experienced AEs and SAEs were similar with both doses of fingolimod and placebo; the occurrence remained similar in the larger patient population exposed to fingolimod 0.5 mg in the All Studies group (Table 2). Fingolimod 1.25-0.5 mg was associated with a higher proportion of SAEs than fingolimod 0.5 mg in the All Studies group. The relative risk of liver enzyme elevations, migraine, lymphopenia, bronchitis, back pain and diarrhoea was slightly higher with fingolimod 0.5 mg than with placebo (Figure 2). A similar proportion

Table 1 Overall exposure to fingolimod after randomization in the All Studies group.

	Fingolimod 5.0/1.25/0.5 mg[a,b] (n=137)	Fingolimod 1.25/0.5 mg[b] (n=1776)	Fingolimod 0.5 mg (n=1640)	Total All Studies group (n=3553)
Patients by exposure intervals, n (%)				
≥6 months	118 (86.1)	1538 (86.6)	1484 (90.5)	3140 (88.4)
≥1 year	108 (78.8)	1400 (78.8)	1360 (82.9)	2868 (80.7)
≥2 years	96 (70.1)	1068 (60.1)	1083 (66.0)	2247 (63.2)
≥3 years	85 (62.0)	708 (39.9)	717 (43.7)	1510 (42.5)
≥5 years	65 (47.4)	75 (4.2)	0 (0)	140 (3.9)
≥7 years	11 (8.0)	19 (1.1)	0 (0)	30 (0.8)
Patient-years of exposure[c]	566.2	4385.3	4118.9	9070.4
Exposure duration, days				
Mean	1509.6	901.9	917.3	932.4
Median	1542	890	966	930

FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; TRANSFORMS, Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis.
Fingolimod exposure in the phase 2 study, and FREEDOMS, FREEDOMS II, TRANSFORMS studies and their ongoing extensions up to the cut-off of 31 March 2011. Duration of exposure was defined as the number of days on fingolimod, starting from the day of initiation of randomized study medication until the day of last dose; days when a patient did not take fingolimod (e.g., temporary interruption of randomized study medication) were excluded. Patients randomized to control drug were included once they had converted to fingolimod in open-label extensions.
[a]Patients initially randomized to fingolimod 5.0 mg during the phase 2 core study or extension were switched to fingolimod 1.25 mg during months 15–24 of the extension phase, and between months 24 and 60 were switched to fingolimod 0.5 mg following assessment of the relative benefit-to-risk profile of both doses.
[b]Patients initially randomized to 1.25 mg during the phase 3 core studies or extensions were switched to fingolimod 0.5 mg following assessment of the relative benefit-to-risk profile of both doses.
[c]Patient-years of exposure was calculated as the sum of the number of days on study drug for all patients divided by 365.25.

of AEs leading to study drug discontinuation occurred with placebo and fingolimod 0.5 mg, but at a higher frequency in patients receiving fingolimod 1.25 mg/1.25-0.5 mg (FREEDOMS group and All Studies group; Table 2). The most common reason for discontinuation due to AEs in FREEDOMS was for AEs related to laboratory tests (fingolimod 0.5 mg, 3.8%; placebo, 1.7%), primarily liver enzyme elevations.

3.2.1. Mortality

No deaths occurred among patients receiving fingolimod 0.5 mg in the FREEDOMS study. For total deaths, data are presented beyond the cut-off point for the All Studies group to be more inclusive. Nineteen deaths had occurred, as of 31 October 2011, in the total MS clinical development programme, which included ongoing, blinded studies in addition to those in the All Studies group. Of these 19 deaths, four occurred in patients receiving placebo (out of 866 patients with 1305 patient-years of exposure) and two occurred before randomization. Of the remaining 13 deaths (out of 3553 patients exposed to fingolimod with 9070 patient-years of exposure), the maximal dose taken was 5 mg for one patient, 1.25 mg for nine patients, and 0.5 mg for three patients (Supplementary Table 1). Five patients had ceased medication 3–36 months before death (one case each of breast cancer, ovarian adenocarcinoma, lymphoma, aspiration pneumonia and MS progression with aspiration pneumonia). Of the remaining eight cases that occurred while still on therapy, or having recently discontinued fingolimod treatment, there were three cases of suicide, and one each of myocardial infarction, road traffic accident, herpes simplex encephalitis, primary disseminated herpes zoster and rapidly deteriorating primary progressive MS; see Supplementary Table 1 for details. In the post-marketing setting, 18 deaths have been reported as of December 2011 from approximately 25,000 patients treated with fingolimod (~15,000 patient-years of exposure) (Supplementary Table 2). Of these deaths, causes included progressive MS (n=5), suicide (n=3), myocardial infarction/cardiac arrest (n=3), sudden unexplained death (n=2; including one patient within 24 h of receiving first dose of fingolimod), drowning (n=2), and one case each of convulsion, culture-negative fungal encephalitis and multi-organ failure; see Supplementary Table 2 for details.

3.3. Cardiovascular effects

The effect of fingolimod on heart rate and atrioventricular (AV) conduction during treatment initiation will be discussed in full detail in a separate manuscript (DiMarco et al., 2012, in preparation). Initiation of fingolimod treatment was associated with transient dose-dependent reductions in heart rate that returned to baseline levels by 1 month after treatment initiation. In the 6 h following treatment initiation, symptomatic bradycardia events were observed in

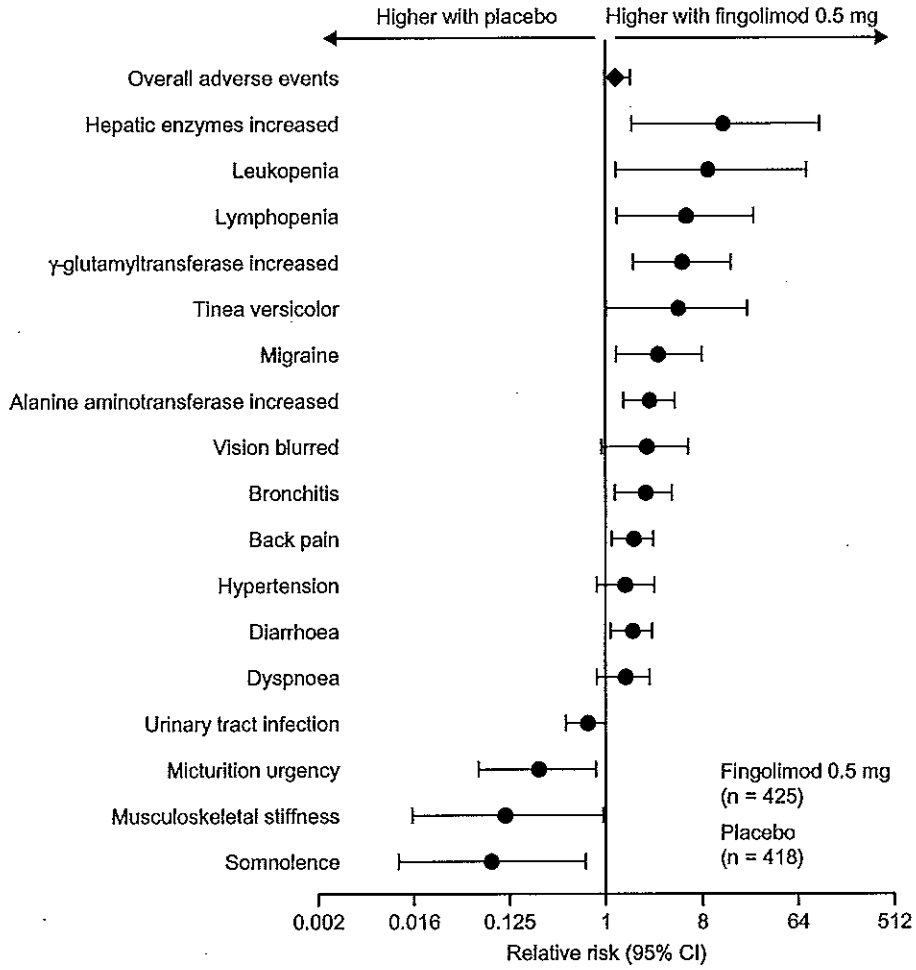


Figure 2 The relative risk of adverse events with fingolimod 0.5 mg compared with placebo in the FREEDOMS group. The relative risk of each AE was calculated by dividing the incidence of the AE in patients receiving fingolimod 0.5 mg by the incidence of the AE in patients receiving placebo. AE, adverse event; CI, confidence interval; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis.

9/1640 (0.5%) and 29/1642 (1.8%) patients who received first-dose fingolimod 0.5 mg and 1.25 mg, respectively. AV conduction abnormalities associated with fingolimod first dosing were uncommon, typically transient, asymptomatic, usually did not require treatment and resolved within the first 24 h on treatment. Second-degree AV blocks, usually Mobitz type I (Wenckebach) were observed in 2/1640 patients (0.1%) receiving fingolimod 0.5 mg in clinical trials.

Cardiac disorder AEs were reported in similar proportions of patients receiving fingolimod 0.5 mg (5.9%; 25/425) or placebo (5.5%; 23/418) over 24 months in the FREEDOMS group, and at a higher rate in patients receiving fingolimod 1.25 mg (8.9%; 38/429). No serious cardiovascular events were observed with fingolimod 0.5 mg in the clinical development programme; three myocardial infarctions occurred in patients receiving placebo (n=2) or interferon beta-1a IM (n=1), and four in the fingolimod 1.25 mg group.

In the All Studies group, patients treated with fingolimod experienced small mean increases of 3 mmHg in systolic blood pressure and 1 mmHg in diastolic blood pressure, which were evident by month 2, increased to month 6 and were largely stable thereafter. Notably high or notable increases in systolic or diastolic blood pressure and hypertension AEs were more frequently reported for fingolimod 1.25-0.5 mg than for fingolimod 0.5 mg (Table 3).

3.3.1. Vascular events

Rare cases of vascular events have occurred in patients treated with fingolimod 1.25 mg or 5.0 mg in the All Studies group, including ischaemic and haemorrhagic strokes (n=3), peripheral arterial occlusive disease (n=2) and posterior reversible encephalopathy syndrome (PRES; n=1). Three cases of PRES have occurred with fingolimod 0.5 mg, two of which were reported in the post-marketing setting as of December 2011; representing a total of three cases in more than 36,000 patients who have ever received fingolimod.

3.4. Liver enzyme effects

Dose-dependent increases in alanine aminotransferase (ALT) levels were observed for fingolimod in the FREEDOMS group and the All Studies group (Table 3). Liver transaminase

Table 2 Adverse event experience in the FREEDOMS and All Studies groups.

Event, *n* (%)	FREEDOMS core study			All Studies	
	Placebo (*n*=418)	Fingolimod 0.5 mg (*n*=425)	Fingolimod 1.25 mg (*n*=429)	Fingolimod 0.5 mg (*n*=1640)	Fingolimod 1.25-0.5 mg (*n*=1776)
At least one AE	387 (92.6)	401 (94.4)	404 (94.2)	1571 (95.8)	1706 (96.1)
Any serious AE	56 (13.4)	43 (10.1)	51 (11.9)	256 (15.6)	316 (17.8)
Death[a]	2 (0.5)	0 (0)	1 (0.2)	4 (0.2)	8 (0.5)
AE leading to study drug discontinuation[b]	24 (5.7)	15 (3.5)	31 (7.2)	124 (7.6)	196 (11.0)
Abnormal laboratory value leading to study drug discontinuation	5 (1.2)	20 (4.7)	32 (7.5)	79 (4.8)	117 (6.6)
AEs occurring in >10% of patients in any treatment group					
Headache	96 (23.0)	107 (25.2)	114 (26.6)	435 (26.5)	455 (25.6)
Nasopharyngitis	115 (27.5)	115 (27.1)	112 (26.1)	498 (30.4)	558 (31.4)
Upper respiratory tract infection	73 (17.5)	73 (17.2)	62 (14.5)	314 (19.1)	358 (20.2)
ALT increased	16 (3.8)	43 (10.1)	50 (11.7)	151 (9.2)	189 (10.6)
Fatigue	45 (10.8)	48 (11.3)	47 (11.0)	176 (10.7)	231 (13.0)
Back pain	29 (6.9)	50 (11.8)	45 (10.5)	197 (12.0)	239 (13.5)
Cough	34 (8.1)	43 (10.1)	37 (8.6)	210 (12.8)	237 (13.3)
Diarrhoea	31 (7.4)	50 (11.8)	40 (9.3)	223 (13.6)	224 (12.6)
Influenza	41 (9.8)	55 (12.9)	40 (9.3)	210 (12.8)	207 (11.7)
Lymphopenia	-	-	-	196 (12.0)	273 (15.4)
Urinary tract infection	47 (11.2)	34 (8.0)	21 (4.9)	199 (12.1)	191 (10.8)
Serious AEs[c]					
Basal cell carcinoma	2 (0.5)	4 (0.9)	1 (0.2)	26 (1.6)	17 (1.0)
Bradycardia	1 (0.2)	4 (0.9)	3 (0.7)	6 (0.4)	24 (1.4)
Multiple sclerosis relapse	1 (0.2)	2 (0.5)	3 (0.7)	13 (0.8)	13 (0.7)
Urinary tract infection	0 (0)	2 (0.5)	0 (0)	4 (0.2)	3 (0.2)
Non-cardiac chest pain	2 (0.5)	2 (0.5)	0 (0)	4 (0.2)	1 (0.1)
Back pain	1 (0.2)	2 (0.5)	0 (0)	3 (0.2)	3 (0.2)
Chest pain	0 (0)	2 (0.5)	0 (0)	4 (0.2)	2 (0.1)
Macular oedema	0 (0)	0 (0)	3 (0.7)	3 (0.2)	9 (0.5)
Epilepsy	0 (0)	0 (0)	2 (0.5)	2 (0.1)	2 (0.1)
Depression	1 (0.2)	0 (0)	2 (0.5)	0 (0)	7 (0.4)
Headache	0 (0)	0 (0)	2 (0.5)	0 (0)	4 (0.2)
Lymphopenia	0 (0)	0 (0)	2 (0.5)	3 (0.2)	8 (0.5)
Liver function test abnormal	1 (0.2)	0 (0)	2 (0.5)	0 (0)	2 (0.1)
First-degree AV block	0 (0)	0 (0)	1 (0.2)	1 (0.1)	6 (0.3)
Second-degree AV block	1 (0.2)	0 (0)	1 (0.2)	1 (0.1)	9 (0.5)
Palpitations	1 (0.2)	0 (0)	1 (0.2)	0 (0)	5 (0.3)
Vertigo	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.2)
Cholelithiasis	1 (0.2)	0 (0)	0 (0)	7 (0.4)	4 (0.2)
Appendicitis	1 (0.2)	0 (0)	0 (0)	5 (0.3)	5 (0.3)
Herpes zoster	0 (0)	0 (0)	0 (0)	2 (0.1)	6 (0.3)
Malignant melanoma	1 (0.2)	0 (0)	1 (0.2)	4 (0.2)	4 (0.2)
Breast cancer	3 (0.7)	0 (0)	1 (0.2)	5 (0.3)	5 (0.3)
Uterine leiomyoma	0 (0)	1 (0.2)	0 (0)	6 (0.4)	3 (0.2)

AE, adverse event; ALT, alanine aminotransferase; AV, atrioventricular; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis.

[a]Deaths in the All Studies group were reported up to the cut-off date of 31 October 2011.

[b]Includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an AE (including abnormal laboratory findings).

[c]Serious AEs experienced by >1 patient in any fingolimod group in the FREEDOMS group or >2 in any fingolimod group in the All Studies group.

Table 3 Special interest adverse events and laboratory abnormalities.

Event, *n* (%)	FREEDOMS core study			All Studies	
	Placebo (*n*=418)	Fingolimod 0.5 mg (*n*=425)	Fingolimod 1.25 mg (*n*=429)	Fingolimod 0.5 mg (*n*=1640)	Fingolimod 1.25-0.5 mg (*n*=1776)
Infections					
At least one infection AE	301 (72.0)	304 (71.5)	294 (68.5)	1222 (74.5)	1291 (72.7)
Infections (events per 100 patient-years)[a]	128.1	126.9	123.0	114.7	118.7
Any severe infection	13 (3.1)	12 (2.8)	15 (3.5)	93 (5.2)	88 (5.4)
Any serious infection	8 (1.9)	7 (1.6)	11 (2.6)	48 (2.9)	61 (3.4)
Infections of interest					
LRTI and lung infections	25 (6.0)	41 (9.6)	49 (11.4)	217 (13.2)	236 (13.3)
Any herpes infection	33 (7.9)	37 (8.7)	25 (5.8)	184 (11.2)	200 (11.3)
Herpes infection SAEs	0	1 (0.2)	1 (0.2)	6 (0.4)	13 (0.7)
Herpes zoster AEs	4 (1.0)	7 (1.6)	3 (0.7)	49 (3.0)	51 (2.9)
Macular oedema					
Patients with assessments	413	423	420	1612	1710
Patients with confirmed macular oedema[b]	0 (0)	0 (0)	7 (1.7)	7 (0.4)	19 (1.1)
Patients treated for macular oedema[b]	0 (0)	0 (0)	5 (1.2)	4 (0.2)	5 (0.3)
Malignancies	10 (2.4)	4 (0.9)	4 (0.9)	49 (3.0)	38 (2.1)
Basal cell carcinoma	3 (0.7)	4 (0.9)	1 (0.2)	30 (1.8)	19 (1.1)
Squamous cell carcinoma of the skin	0 (0)	0 (0)	1 (0.2)	1 (0.1)	1 (0.1)
Malignant melanoma	1 (0.2)	0 (0)	1 (0.2)	4 (0.2)	4 (0.2)
Breast cancer	3 (0.7)	0 (0)	1 (0.2)	5 (0.3)	5 (0.3)
Cervix carcinoma	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Endometrial carcinoma	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Prostate cancer	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Ovarian epithelial cancer	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)
Liver enzyme and bilirubin elevations[c]					
ALT elevation					
≥ 3 × ULN	7 (1.7)	36 (8.5)	53 (12.5)	147 (9.0)	213 (12.2)
≥ 5 × ULN	4 (1.0)	8 (1.9)	13 (3.1)	32 (2.0)	50 (2.9)
≥ 10 × ULN	0 (0)	1 (0.2)	0 (0)	3 (0.2)	7 (0.4)
Bilirubin					
≥ 1 × ULN	39 (9.4)	47 (11.1)	42 (9.9)	142 (8.7)	158 (9.0)
Increased blood pressure					
Systolic blood pressure					
≥ 160 mmHg	6 (1.4)	8 (1.9)	19 (4.4)	78 (4.8)	118 (6.6)
≥ 20 mmHg increase from baseline	76 (18.2)	92 (21.6)	112 (26.1)	560 (34.1)	706 (39.8)
Diastolic blood pressure					
≥ 100 mmHg	17 (4.1)	31 (7.3)	29 (6.8)	125 (7.6)	191 (10.8)
≥ 15 mmHg increase from baseline	84 (20.1)	93 (21.9)	113 (26.3)	486 (29.6)	597 (33.6)
Hypertension AE	16 (3.8)	26 (6.1)	27 (6.3)	145 (8.8)	200 (11.3)

AE, adverse event; ALT, alanine aminotransferase; LRTI, lower respiratory tract infection; SAE, serious adverse event; ULN, upper limit of normal.

[a]The incidence of infections per 100 patient-years was calculated as the number of infections divided by the patient-years in the treatment group, multiplied by 100. The patient-year denominator was defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

[b]The proportion of patients with macular oedema assessments was used as the denominator.

[c]Number of patients with laboratory assessments in the FREEDOMS group: placebo, *n*=414; fingolimod 0.5 mg, *n*=424; fingolimod 1.25 mg, *n*=425. Number of patients with laboratory assessments in the All Studies group: fingolimod 0.5 mg, *n*=1633; fingolimod 1.25 mg, *n*=1753.

elevations were asymptomatic in most patients and most frequently occurred within the first 6-9 months of treatment. There were no cases of severe drug-induced hepatotoxicity during clinical trials or in the post-marketing setting.

3.5. Macular oedema

No cases of macular oedema occurred in patients receiving fingolimod 0.5 mg in the FREEDOMS group. Confirmed macular oedema was reported in 0.4% (7/1640) and 1.1% (19/1776) of patients treated with fingolimod 0.5 mg and 1.25-0.5 mg, respectively, in the All Studies group (Table 3). The majority (65%) were diagnosed in the first 6 months of receiving fingolimod, with approximately one-third requiring treatment and virtually universal recovery after treatment cessation (Calabresi et al., in press; Cohen et al., 2010; Kappos et al., 2006, 2010; Zarbin et al., 2011).

3.6. Infections

In FREEDOMS, the overall incidence of infections was similar in patients receiving fingolimod 0.5 mg, 1.25 mg or placebo (Table 3). Serious infections occurred in similar proportions of patients receiving fingolimod 0.5 mg or placebo, and at a higher rate with fingolimod 1.25 mg. The incidence of lower respiratory tract infections (mainly bronchitis) was slightly increased with fingolimod compared with placebo and appeared to be dose-dependent (Table 3). For herpes viral infections, the incidence was similar among patients treated with fingolimod 0.5 mg or placebo, but higher in the All Studies group, who were given longer follow-up. The incidence of herpes viral infections reported as SAEs was low in all treatment groups in FREEDOMS (Table 3). A fatal primary varicella zoster infection and fatal herpes simplex encephalitis occurred in two patients who had been treated with fingolimod 1.25 mg in the All Studies group, and have been previously reported (Cohen et al., 2010).

3.7. Lymphopenia

In the All Studies group, after 1 month of treatment the mean lymphocyte count was reduced by 73% from baseline values to 0.49×10^9/L (n=1505) in the fingolimod 0.5 mg group and by 77% to 0.41×10^9/L (n=1575) in the fingolimod 1.25-0.5 mg group. Values then remained stable during chronic treatment. The incidence of lymphopenia as an AE was higher in the fingolimod 1.25-0.5 mg group than in the 0.5 mg group (Table 2). In FREEDOMS 18% of patients (78/425) on 0.5 mg experienced a mean lymphocyte count of $<0.2 \times 10^9$/L on any single occasion and 0.7% (3/425) had a count of $<0.1 \times 10^9$/L on any single occasion. Re-testing was conducted at local laboratories, so the number of patients with confirmed counts below these values (and thus requiring dose interruption) was not reported. Analysis of infections by nadir lymphocyte count did not show an increase in fingolimod-treated patients compared with placebo (reviewed in detail previously) (Francis et al., 2014).

3.8. Malignancies

The overall incidence of malignancies was not increased in fingolimod-treated patients (0.9% in both dose groups) compared with patients who received placebo (2.4%) in the FREEDOMS group, and results were similar for the All Studies group (Table 3). A trend towards an increased incidence of basal cell carcinoma has been noticed in the All Studies group. Three lymphoma cases (cutaneous T-cell lymphoma, large B-cell non-Hodgkin lymphoma and Epstein-Barr virus-positive B-cell lymphoma) have been reported in fingolimod-treated patients in the clinical development programme (up to December 2011) in studies that were not included in the All Studies group because they were still ongoing without a cleaned or locked database.

4. Discussion

The safety profile of fingolimod has been well characterized in the MS clinical development programme, with the All Studies group consisting of 3553 fingolimod-treated patients with MS and more than 9070 patient-years of exposure (as of 31 March 2011). The overall incidence of AEs and SAEs was similar in patients who received the approved dose of fingolimod (0.5 mg) in the All Studies and FREEDOMS groups, and those who received placebo in the FREEDOMS group. Fingolimod was, however, associated with dose-dependent increases in the incidence of certain specific AEs, including transient, mostly asymptomatic reductions in heart rate, blood pressure increases, macular oedema and liver enzyme elevations. However, the similar rate of study drug discontinuation due to AEs among patients receiving fingolimod 0.5 mg (All Studies and FREEDOMS groups) and placebo (FREEDOMS group) indicates that, with the approved dose, these AEs have a limited impact on tolerability and adherence.

As of December 2011, 31 deaths have been reported in more than 30,000 patients exposed to fingolimod since May 2003; 13 occurring in clinical trials (some at doses higher than the approved 0.5 mg dose) and 18 in the post-marketing setting. No specific pattern of fatalities has been observed. The incidence of all-cause and cardiovascular deaths in patients with MS treated with fingolimod are consistent with an age- and sex-matched general population (Arias, 2011).

One reported death occurred within the first 24 h after taking the first dose of fingolimod, for which the cause of death remains uncertain, despite a complete autopsy examination. This case and 10 other cases (of the total of 31 deaths) of otherwise unexpected or unexplained death occurred at various times after initiating therapy with fingolimod. Several of the post-marketing cases lack sufficient information to determine cause of death or relationship to fingolimod therapy. Following review of these cases and the overall cardiac safety data for fingolimod by the US Food and Drug Administration and European Medicines Agency, a relationship between these events and fingolimod has not been established (European Medicines Agency, 2012; US Food and Drug Administration, 2011, 2012a, 2012b). The number of deaths of apparent cardiovascular or unknown origin is similar to that seen in patients with MS not treated

with fingolimod (US Food and Drug Administration, 2012b). Nevertheless, as a precautionary measure, revised guidelines relating to the use of fingolimod in patients with cardiac risk factors, including more rigorous first-dose monitoring, have been included in the prescribing information worldwide.

The initiation of fingolimod was associated with a transient, dose-dependent reduction in heart rate, including infrequent conduction delay, which was usually asymptomatic. These effects are not unexpected because they are likely to be mediated by modulation of S1PRs in atrial myocytes, and in sinus and AV nodal cells (Koyrakh et al., 2005). However, tolerance rapidly develops to these effects due to internalization of the receptors. Owing to the potential risk of rhythm disturbances, fingolimod should not be used in patients with second-degree Mobitz type II or higher AV blocks, sick-sinus syndrome or sino-atrial heart block, or in patients with QT prolongation or who are receiving drugs that have a known association with the development of torsades de pointes (European Medicines Agency, 2012; US Food and Drug Administration, 2012a).

Additionally, while there is no clear relationship between fingolimod and sudden death, patients with cardiac risk factors (known ischaemic heart disease, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnoea) should not be commenced on fingolimod because significant bradycardia may be poorly tolerated in these patients (European Medicines Agency, 2012; US Food and Drug Administration, 2012a).

The mechanism for the increase in blood pressure is not completely clear, but is potentially the result of unopposed natural sphingosine 1-phosphate ligand stimulation of S1PR type 2/3 ($S1P_{2/3}$) endothelial receptors, owing to the strong functional antagonism of $S1P_1$ by fingolimod (Brinkmann et al., 2010).

The mechanism for the increased incidence of elevations in liver transaminases with fingolimod 0.5 mg compared with placebo also remains unclear. Liver enzyme elevations generally returned to normal or almost normal within a few months of stopping therapy.

Confirmed macular oedema occurs in less than 0.5% of patients receiving fingolimod 0.5 mg. Patients with a history of uveitis have an increased risk of macular oedema (Zarbin et al., 2011, 2013). The mechanism for the development of macular oedema in patients receiving fingolimod may also be related to the role of the S1PR in the regulation of endothelial barriers (Brinkmann, 2007; Marsolais and Rosen, 2009).

The observed reductions in peripheral blood lymphocyte counts are an expected pharmacodynamic outcome of fingolimod therapy, which causes reversible retention of lymphocytes in the lymph nodes, and these actions are thought to be integral to the therapeutic effect of fingolimod in MS. This integrated analysis of safety indicates that fingolimod 0.5 mg does not increase the overall risk of infections, including those considered severe or serious, compared with placebo. However, during the clinical trials, a persistent reduction in mean lymphocyte counts below 0.2×10^9/L required dose interruption until counts recovered.The lack of effect on overall infection risk may be related to the selective effect of fingolimod on lymphocyte subsets. Fingolimod treatment specifically retains naïve T cells and central memory T cells in the lymph nodes, while largely sparing effector memory T cells (Mehling et al., 2008, Pham et al., 2008), which have important roles in immune surveillance and memory immune responses (Lanzavecchia and Sallusto, 2000). Although fingolimod leads to the retention of lymphocytes in the lymph nodes, the lymphocytes remain functional and retain their ability to proliferate and differentiate (Brinkmann, 2009; Chun and Hartung, 2010), as might happen in response to viral or bacterial infection. However, some questions remain regarding herpes infections. Different incidences were observed across the phase 2 and 3 studies (Calabresi et al., in press; Cohen et al., 2010; Kappos et al., 2006, 2010), but in this integrated analysis, zoster infections were slightly increased with fingolimod 0.5 mg (3.0%) compared with placebo (1.0%). Additionally, isolated cases of severe zoster infections have been reported, including a fatal case of disseminated primary infection (fingolimod 1.25 mg), a case of polycranial neuritis (Gross et al., 2012), a case of varicella-related encephalitis with vasculopathy (Ratchford et al., 2012) and a recent fatal case of disseminated varicella (data on file). The latter three cases occurred in patients with presumed previous exposure to varicella and who had received fingolimod 0.5 mg (Gross et al., 2012; Ratchford et al., 2012). Antibody status to varicella zoster virus should be checked before starting fingolimod. Vigilance for zoster occurrence and then early treatment is warranted in patients receiving fingolimod.

Beyond the data cut-off dates used in this manuscript, unexpected serious events of note have been reported. Three cases of progressive multifocal leukoencephalopathy (PML) and/or immune reconstitution inflammatory syndrome have been reported but all were related to recent prolonged exposure to natalizumab (Novartis AG, data on file). A case of PML that began 7 months after fingolimod therapy initiation in a patient without prior exposure to natalizumab has been recently reported (Novartis AG, data on file). Two fatal cases of haemophagocytic syndrome (HPS) have been reported to Novartis (Novartis AG, data on file). This rare disorder is characterized by impaired or absent activity of natural killer cells and cytotoxic T cells, leading to cytokine dysregulation with the proliferation and activation of histiocytes (Janka, 2007; Maakaroun et al., 2010). The clinical presentation is one of multi-organ dysfunction and haemophagocytosis within the reticuloendothelial system that is characterized by pancytopenia and organomegaly (Ishii et al., 2007; Maakaroun et al., 2010). Although not fully understood, HPS appears to be the result of an uncontrolled immune response triggered by different immune stimuli, particularly Epstein-Barr virus (de Kerguenec et al., 2001; Ishii et al., 2007; Janka, 2007, 2012; Maakaroun et al., 2010). The role of fingolimod in these cases remains uncertain.

As with any immunodulatory agent, the effect of fingolimod on the immune system might confer an increased risk of malignancy; however, the results of FREEDOMS and the larger All Studies analysis indicate that the overall incidence is not increased in patients receiving fingolimod compared with those receiving placebo. A slight imbalance regarding basal cell carcinoma continues to be evaluated in the post-marketing setting. The occurrence of three cases of lymphoma in the overall clinical development programme is in line with epidemiological data reporting the background

incidence of lymphoma (19.1 cases per 100,000 person-years) (Alexander et al., 2007). However, because of the low incidence of malignancies and the limited scope and duration of exposure, firm conclusions on an increased risk of malignancies with fingolimod cannot yet be drawn.

The major strengths of the present analysis include direct comparison with placebo in the FREEDOMS group, and the large number of patients receiving fingolimod at the licensed dose (0.5 mg, n=1640) or above in the All Studies group. The safety data from FREEDOMS II yield similar results to those of FREEDOMS, with the exception of a slightly higher rate of basal cell carcinoma and herpes zoster in the treated groups (Calabresi et al., in press). The exposure to fingolimod in the All Studies group was over 9070 patient-years, and 140 patients had received the drug for at least 5 years without the emergence of new AEs of interest. Given the exposure to fingolimod, the incidence of any event not observed to date will be less than 1 in 3300 patient-years (Eypasch et al., 1995; Hanley and Lippman-Hand, 1983). An important caveat of the All Studies analysis is the absence of a control group, necessitating indirect comparisons with 2-year data from the placebo arm of the FREEDOMS study.

5. Conclusions

This large-scale analysis provides further information regarding the safety profile of fingolimod. The approved dose is generally well tolerated in patients with relapsing MS, although infrequent SAEs can occur. Additional long-term observation of the safety profile, in particular monitoring of infections, malignancies and cardiovascular complications in the post-marketing setting, will be obtained via post-approval, long-term follow-up and safety studies, and pharmacovigilance. This will help to consolidate the safety profile of this therapy further.

Role of funding source

The study was funded by Novartis Pharma AG, Basel, Switzerland.

Conflict of interest statements

Prof. Kappos has participated as Principal Investigator, Member or Chair of planning and steering committees or advisory boards in corporate-sponsored clinical trials in MS and other neurological diseases. The sponsoring pharmaceutical companies for these trials include Actelion, Advancell, Allozyne, BaroFold, Bayer Health Care Pharmaceuticals, Bayer Schering Pharma, Bayhill, Biogen Idec, BioMarin, CLC Behring, Elan, Genmab, GeNeuro SA, Genmark, GlaxoSmithKline, Lilly, Merck Serono, MediciNova, Novartis, Novo Nordisk, Peptimmune, Sanofi-Aventis, Santhera, Roche, Teva, UCB and Wyeth. Prof. Kappos has also received funding for speaker activities in the form of non-restricted educational grants from several of the above listed companies. Honoraria and other payments for all these activities have been exclusively used for funding of research in his department. Research and the clinical operations (nursing and patient care services) of the MS Center in Basel have been supported by non-restricted grants from one or more of these companies and by grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, and the Gianni Rubatto, Novartis and Roche Research Foundations.

Dr. Cohen has received personal compensation for serving as a Consultant or Speaker from EMD Serono, Genzyme, Innate Immunotherapeutics and Novartis. Dr. Cohen has received research support paid to his institution from Biogen Idec, Consortium of MS Centers, US Department of Defense, Genzyme, US National Institute of Health, National MS Society (USA), Novartis, Receptos, Synthon and Teva.

Drs. Collins, de Vera, Zhang-Auberson and von Rosenstiel are employees of Novartis Pharma AG, Basel, Switzerland.

Dr. Francis and S. Ritter are employees of Novartis Pharmaceutical Corporation, East Hanover, NJ, USA.

Contributions

The authors take full responsibility for the content of the paper. All authors had full access to all the study data. All authors were involved in the interpretation of the data and the writing of the paper, and the decision to submit the manuscript for publication.

All authors were involved in analysis and interpretation of the data, and drafting and revising the manuscript for content. W. Collins, A. de Vera, G. Francis, P. von Rosenstiel, J. Cohen and L. Kappos were involved in the design and concept of studies included in this analysis.

The authors thank the patients and investigators who took part in the studies contributing to the analyses presented here. They thank Lee Anne Carroll of Novartis Pharmaceuticals, and Sarah Griffiths and Carolyn Brechin of Oxford PharmaGenesis™ Ltd for editorial assistance, collating the comments of authors and other named contributors, and editing the paper for submission. Such editorial help was funded by Novartis Pharma AG.

Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2014.03.002.

References

Alexander DD, Mink PJ, Adami HO, Chang ET, Cole P, Mandel JS, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer 2007;120(Suppl. 12):S1-39.

Arias E. United States life tables, 2007. Natl Vital Stat Rep 2011;59:1-60.

Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. Pharmacol Ther 2007;115:84-105.

Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol 2009;158:1173-82.

Brinkmann V, Billich A, Baumruker T, Heining P, Schmouder R, Francis G, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat Rev Drug Discov 2010;9:883-97.

Calabresi PA, Radue E-W, Goodin D, Jeffery D, Rammohan K, Reder AT, et al. Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis: results from the 24-month phase 3 double-blind, randomised, placebo-controlled study (FREEDOMS II). Lancet Neurol 2014. http://dx.doi.org/10.1016/S1474-4422(14)70049-3, in press.

Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010;33:91-101.

Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402-15.

Comi G, O'Connor P, Montalban X, Antel J, Radue EW, Karlsson G, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler 2010;16:197-207.

de Kerguenec C, Hillaire S, Molinie V, Gardin C, Degott C, Erlinger S, et al. Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. Am J Gastroenterol 2001;96:852-7.

DiMarco JP, O'Connor P, Cohen JA, Reder AT, Zhang-Auberson L, Tang D, et al. Fingolimod treatment initiation experience: cardiac and Holter electrocardiogram findings from three phase 3 studies. Mult Scler 2012;18(Suppl. 4):S55-277.

DiMarco JP, O'Connor P, Cohen JA, Reder AT, Zhang-Auberson L, Tang D, et al. First-dose effects of fingolimod: pooled safety data from three phase 3 studies 2014. (in preparation).

European Medicines Agency. Annex I. Summary of Product Characteristics. Gilenya (fingolimod). ⟨http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf⟩; 2011 [accessed 30.01.13].

European Medicines Agency. Revised Summary of Product Characteristics. Gilenya (fingolimod). ⟨http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/04/WC500125687.pdf⟩; 2012 [accessed 30.01.13].

Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. Br Med J 1995;311:619-20.

Francis G, Kappos L, O'Connor P, Collins W, Tang D, Mercier F, et al. Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy. Mult Scler 2014;20:471-80.

Gross CM, Baumgartner A, Rauer S, Stich O. Multiple sclerosis rebound following herpes zoster infection and suspension of fingolimod. Neurology 2012;79:2006-7.

Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. J Am Med Assoc 1983;249:1743-5.

Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 2007;86:58-65.

Janka GE. Hemophagocytic syndromes. Blood Rev 2007;21:245-53.

Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med 2012;63:233-46.

Karlsson G, Francis G, Koren G, Heining P, Zhang X, Cohen JA, et al. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. Neurology 2014;82(8):674-80.

Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006;355:1124-40.

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.

Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011;10:520-9.

Koyrakh L, Roman MI, Brinkmann V, Wickman K. The heart rate decrease caused by acute FTY720 administration is mediated by the G protein-gated potassium channel I. Am J Transplant 2005;5:529-36.

Lanzavecchia A, Sallusto F. Dynamics of T lymphocyte responses: intermediates, effectors, and memory cells. Science 2000;290:92-7.

Maakaroun NR, Moanna A, Jacob JT, Albrecht H. Viral infections associated with haemophagocytic syndrome. Rev Med Virol 2010;20:93-105.

Marsolais D, Rosen H. Chemical modulators of sphingosine-1-phosphate receptors as barrier-oriented therapeutic molecules. Nat Rev Drug Discov 2009;8:297-307.

Mehling M, Brinkmann V, Antel J, Bar-Or A, Goebels N, Vedrine C, et al. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. Neurology 2008;71:1261-7.

Novartis AG. Novartis Statement: Gilenya (fingolimod) Safety Information Update. ⟨http://www.novartis.com/downloads/newsroom/product-related-info-center/statement-PML.pdf⟩ [last updated 13.04.12; accessed 30.01.13].

Pham TH, Okada T, Matloubian M, Lo CG, Cyster JG. S1P1 receptor signaling overrides retention mediated by G alpha i-coupled receptors to promote T cell egress. Immunity 2008;28:122-33.

Ratchford JN, Costello K, Reich DS, Calabresi PA. Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod. Neurology 2012;79:2002-4.

US Food and Drug Administration. Gilenya Prescribing Information. ⟨http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022527s002lbl.pdf⟩; 2010 [accessed 30.01.13].

US Food and Drug Administration. Gilenya (fingolimod): Drug Safety Communication - Safety Review of a Reported Death After the First Dose. ⟨http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm284355.htm⟩; 2011 [posted 20.12.11; accessed 30.01.13].

US Food and Drug Administration. Gilenya (fingolimod): Revised US Prescribing Information. ⟨http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022527s008lbl.pdf⟩; 2012a [accessed 30.01.13].

US Food and Drug Administration. Gilenya (fingolimod): Drug Safety Communication - Revised Recommendations for Cardiovascular Monitoring and Use of Multiple Sclerosis Drug Gilenya (fingolimod). ⟨http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm⟩; 2012b [accessed 30.01.13].

Zarbin M, Reder A, Collins W, Francis G, Zhang X, Zhao Y, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Neurology 2011;76:A238.

Zarbin MA, Jampol LM, Jager RD, Reder AT, Francis G, Collins W, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Ophthalmology 2013;120:1432-9.